Medical Genetics

Volume I
Basic Genetics

Part VII
Oncogenetics
Genetics of Cancer

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2022

Spectrum of Medical Genetics

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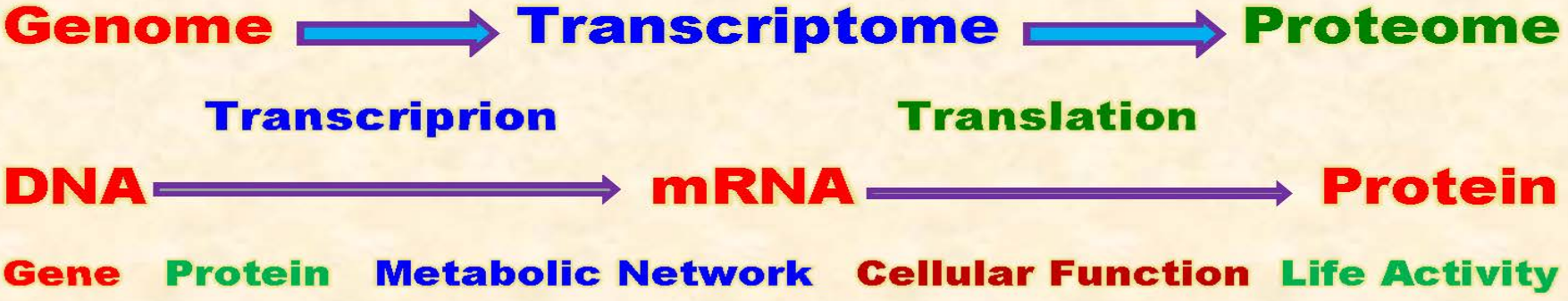
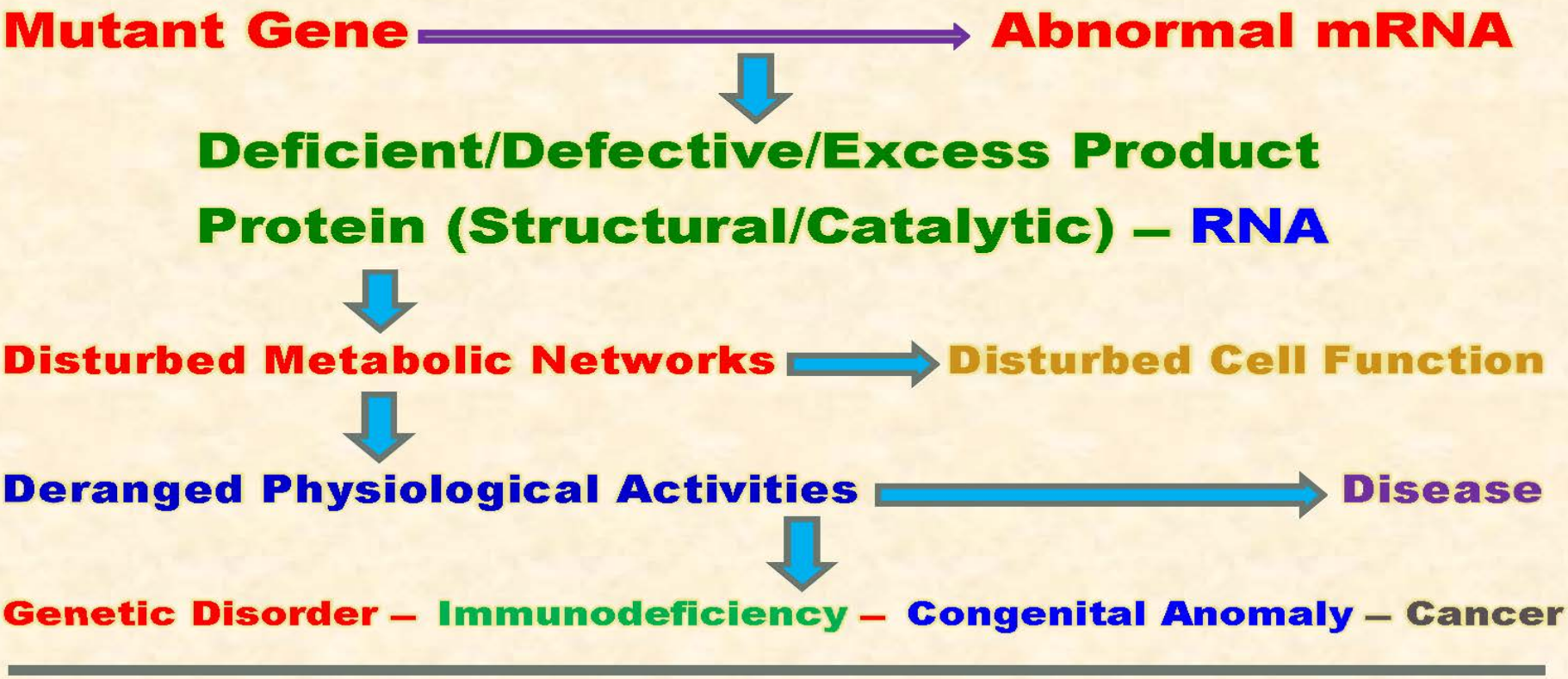
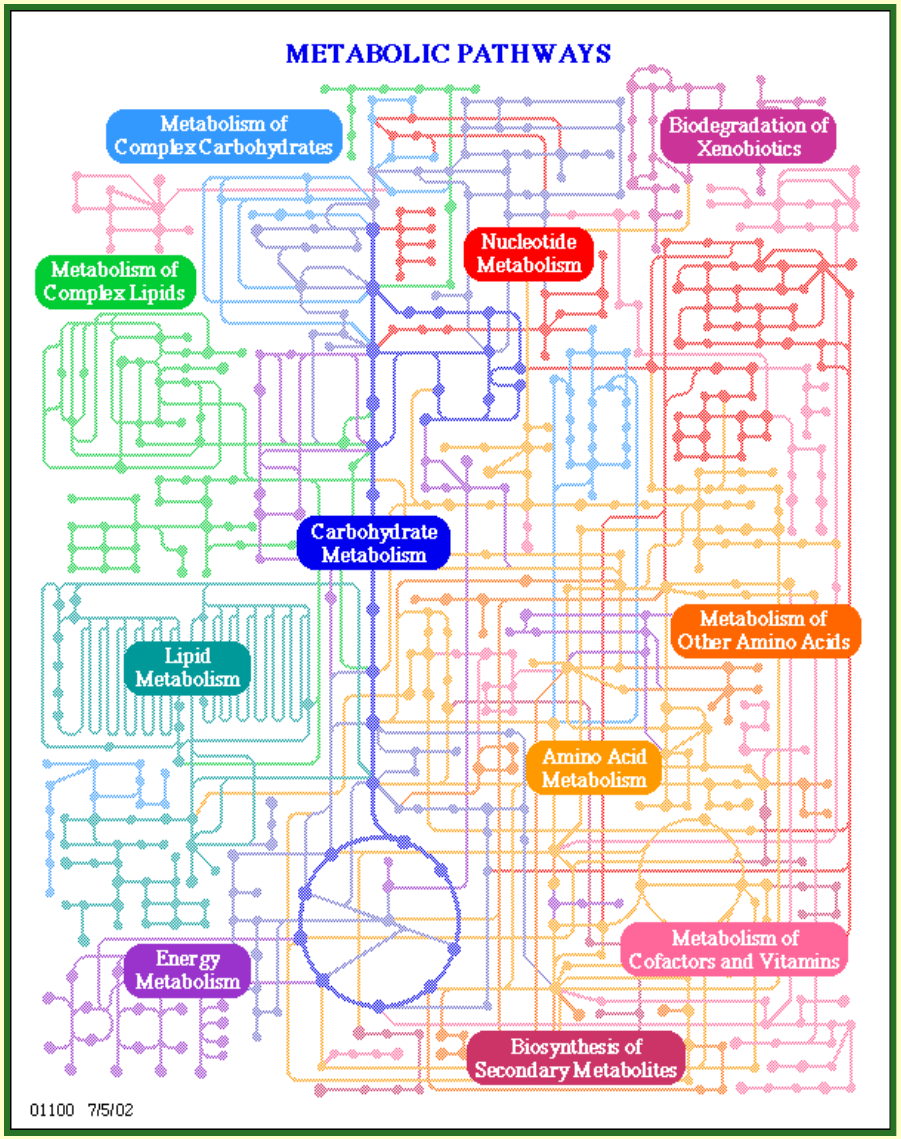
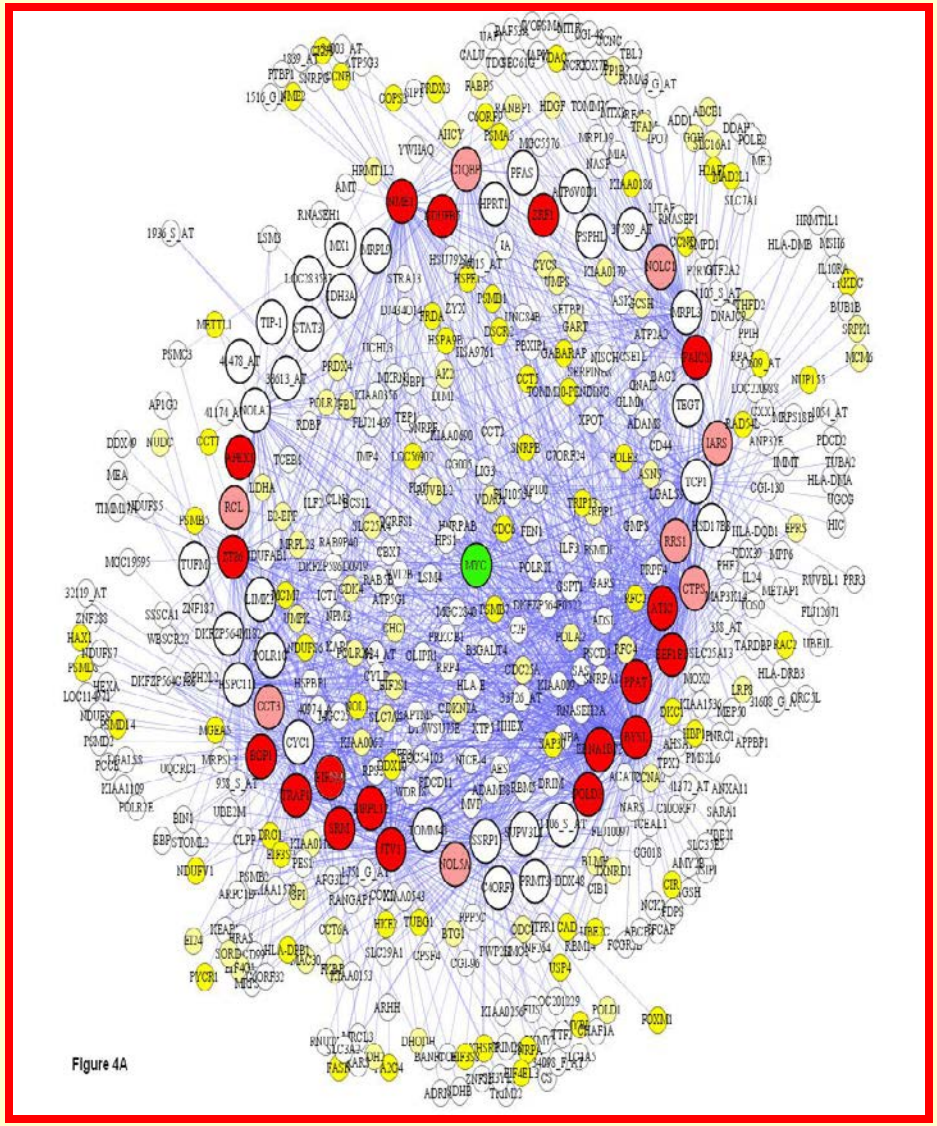
Dogma Of Molecular Pathology In Health And Disease





The Concept Of Metabolic Networks





Nature of malignant transformation

Malignant transformation of normal cells to cancer cells represents an enigmatic phenomenon because of the many ambiguous controversies embodied within most of its aspects. Within a clinical context, cancer with very few exceptions, is a dreadful progressive disease that ends lethally.

Within a biological context, however, cancer is a peculiar biological system that has its own characteristic rules that regulate the actions, interactions, structure and behavior of its various components, irrespective of the normal biological rules that dictate the corresponding aspects in normal cells. Unfortunately, the majority of these cancer-regulating rules are, still, unknown.

Oncogenetics, or genetics of cancer, comprises the study of genetic factors involved in carcinogenesis. These factors include proto-oncogenes or genes which upon mutation convert to oncogenes, or genes that predispose to occurrence of malignant transformation of cells, oncogenic mutagens or carcinogens which are external factors that can lead to development of cancer including carcinogenic chemicals, irradiation and oncogenic viruses, tumor suppressor genes that function in a reverse way to prevent/suppress and restrain malignant transformation of cells under effects of oncogenes or carcinogens, metastasis suppressor genes that function to prevent, arrest, and reduce invasion and metastasis of tumors to neighboring tissues and distant organs, respectively.

Genetic Factors Involved In Carcinogenesis	
A. Genome Instability	1. Reversion to early embryonic developmental stage. 2. Mass activation of dormant/suppressed genes 3. Mass suppression of active functioning genes. 4. Replicative stress leading to double strand breaks (DSB)
B. DNA Protective Genes Metallothioneins Genes Lamin Genes (LMNA gene)	Exposure to External/Internal Mutagens leading to damage of DNA regulatory/protective genes.
C. Proto-Oncogenes Cyclin D1 gene Cyclin E1 gene.	1. Mutation-induced transformation to oncogenes. 2. Enhanced expression of oncogenes. 3. Increased synthesis of oncoproteins/transcription factors/coding & non-coding RNAs.
D. Tumor Suppression Genes (TSG) p53 tumor suppressor gene Retinoblastoma (RB1) tumor suppressor gene	1. Mutation-induced disruption/inactivation of (TSG). 2. Mutation-induced chromosomal deletions of (TSG)
E. DNA Repair Genes (DRG) ATM (Ataxia-Telangiectasia gene) DMC1, XRCC2, RAD52. LMNA Gene	Mutation-induced disruption/inactivation/deletion of (DRG). DNA double strand break repair.
F. Apoptosis Regulatory Genes (ARG) Anti-apoptotic gene Bcl-2 Pro-apoptotic gene Bax	Mutation-induced disruption/inactivation/deletion of (ARG)
G. Metastasis Enhancing Genes Matrix Metalloproteinases (MMP) Genes: Stromelysin 1,2,3 genes Matrilysin 1,2 genes Collagenases genes	Degrade extracellular matrix proteins leading to invasion/metastasis of malignant cells.
H. Antimetastatic genes NM23 gene BMP6 (Bone Morphogenetic Protein 6) gene	Inhibit/decrease ability of malignant cells to break intercellular barriers and invasion of neighboring/distant sites.

Development of Malignant Tumors

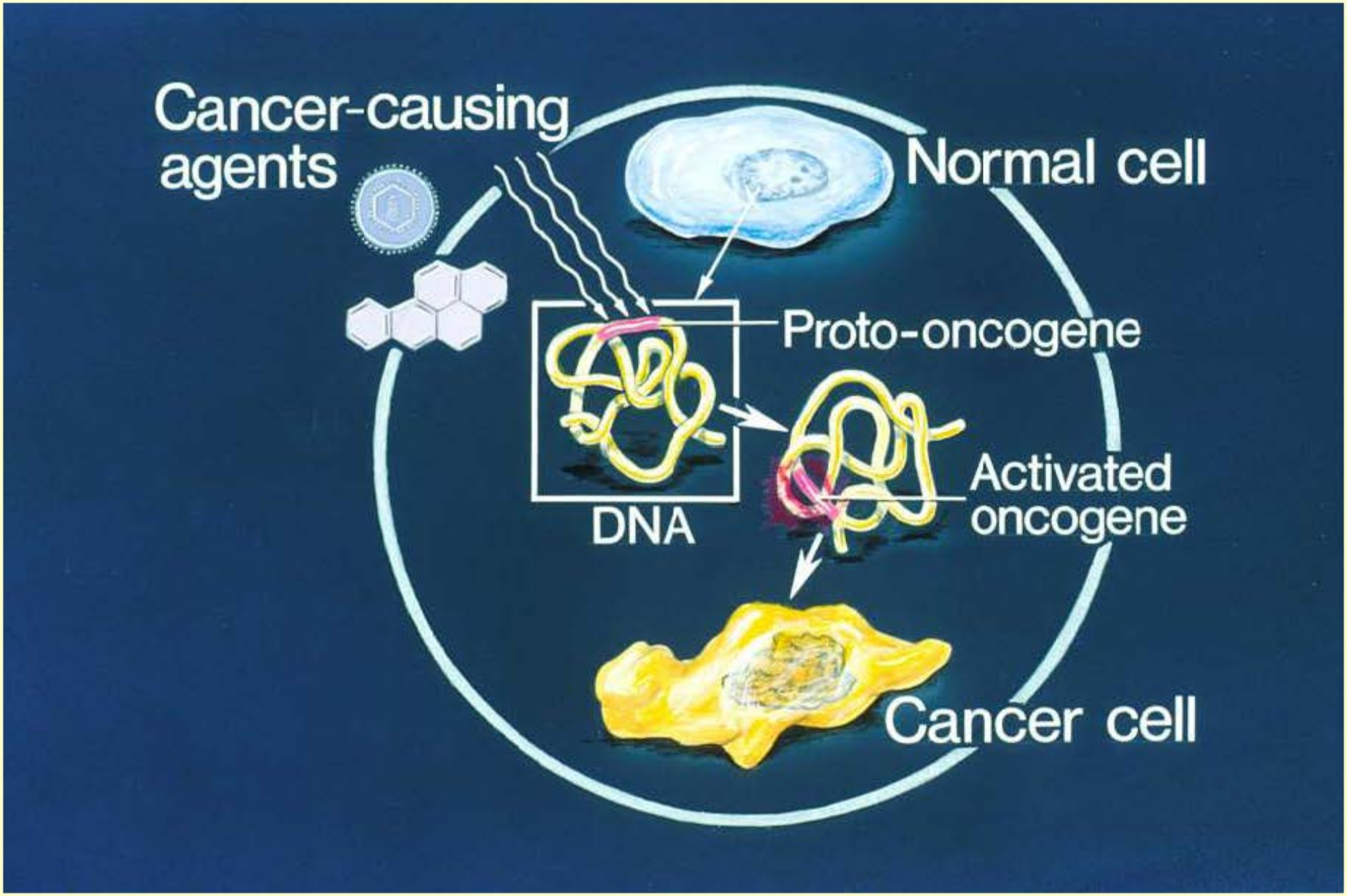
Formation of malignant tumors or carcinogenesis is a genetically-determined complex, progressive, multi-stage process, primarily caused, and starts, by either one of two main mechanisms:

1. Mutation-induced transformation of proto-oncogenes to oncogenes.

2. Mutation-induced disruption or inactivation of tumor-suppressor genes.

In addition to these two main mechanisms of carcinogenesis, many other complementary mechanisms participate in tumor development, tumor growth, invasion of neighboring tissues, and metastasis to distant tissues and organs.

Mechanism Of Induced Malignant Transformation

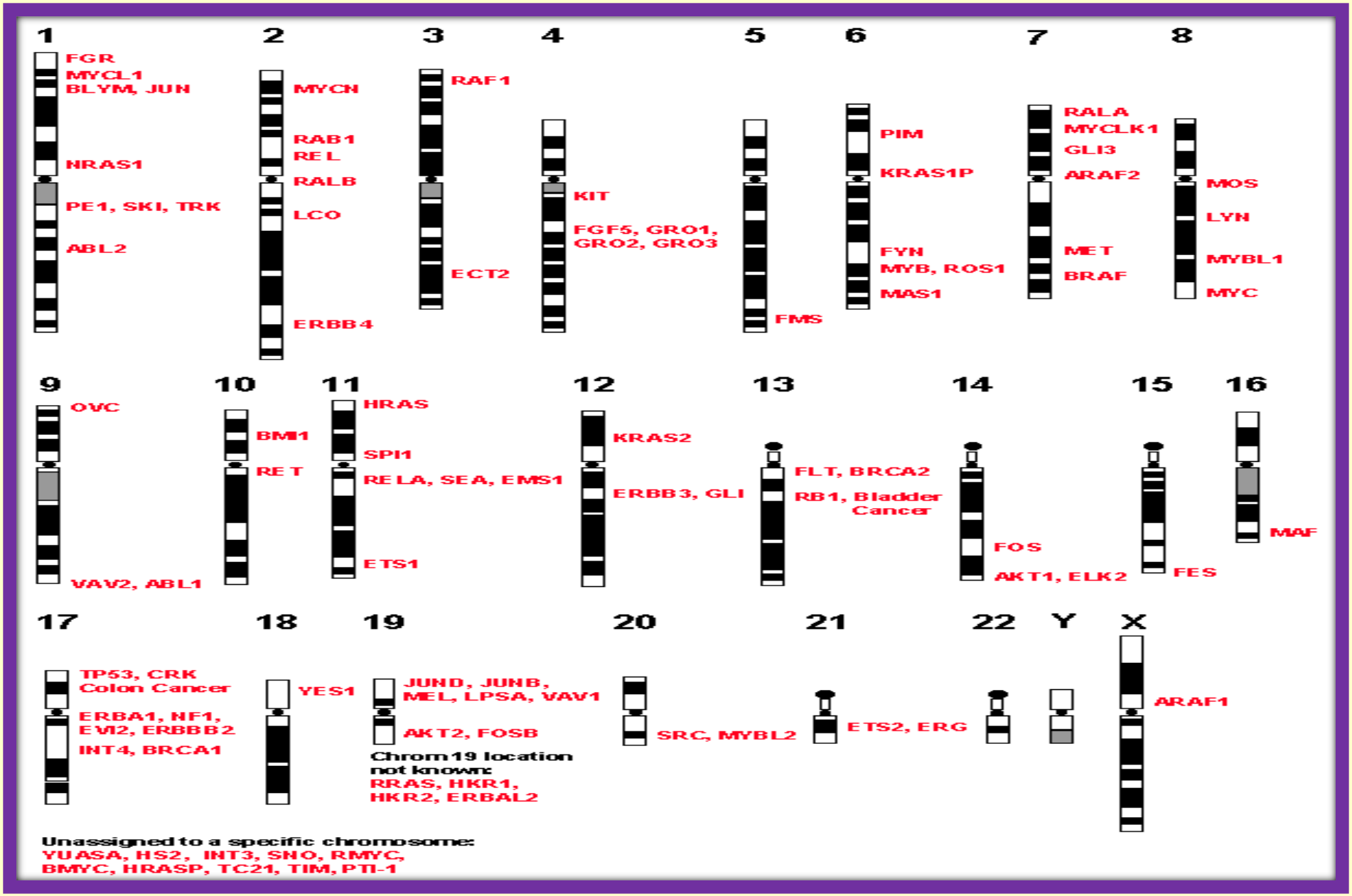


Proto-oncogenes are vital genes widely distributed in most regions of the human genome. They are responsible for surveying and supervising vital essential cellular processes including the cell cycle, cell division, cell differentiation, and cell death.

In addition, the vital importance of Proto-oncogenes stems from their indispensable roles in controlling and regulating other essential and important cell processes.

These processes are crucial for normal structural and functional development and performance of the cell and the organism during all stages of life starting with fertilization, embryogenesis, fetogenesis, and all through post-natal life till death of the cell and the whole organism.

Proto-Oncogenes In The Human Genome



Proto-oncogenes have the characteristics of the three major categories of genes, viz. Master, Structural, and Regulatory genes.

1. Proto-Oncogenes are master genes functioning round the clock from the start of fertilization till the end of life of the cell.

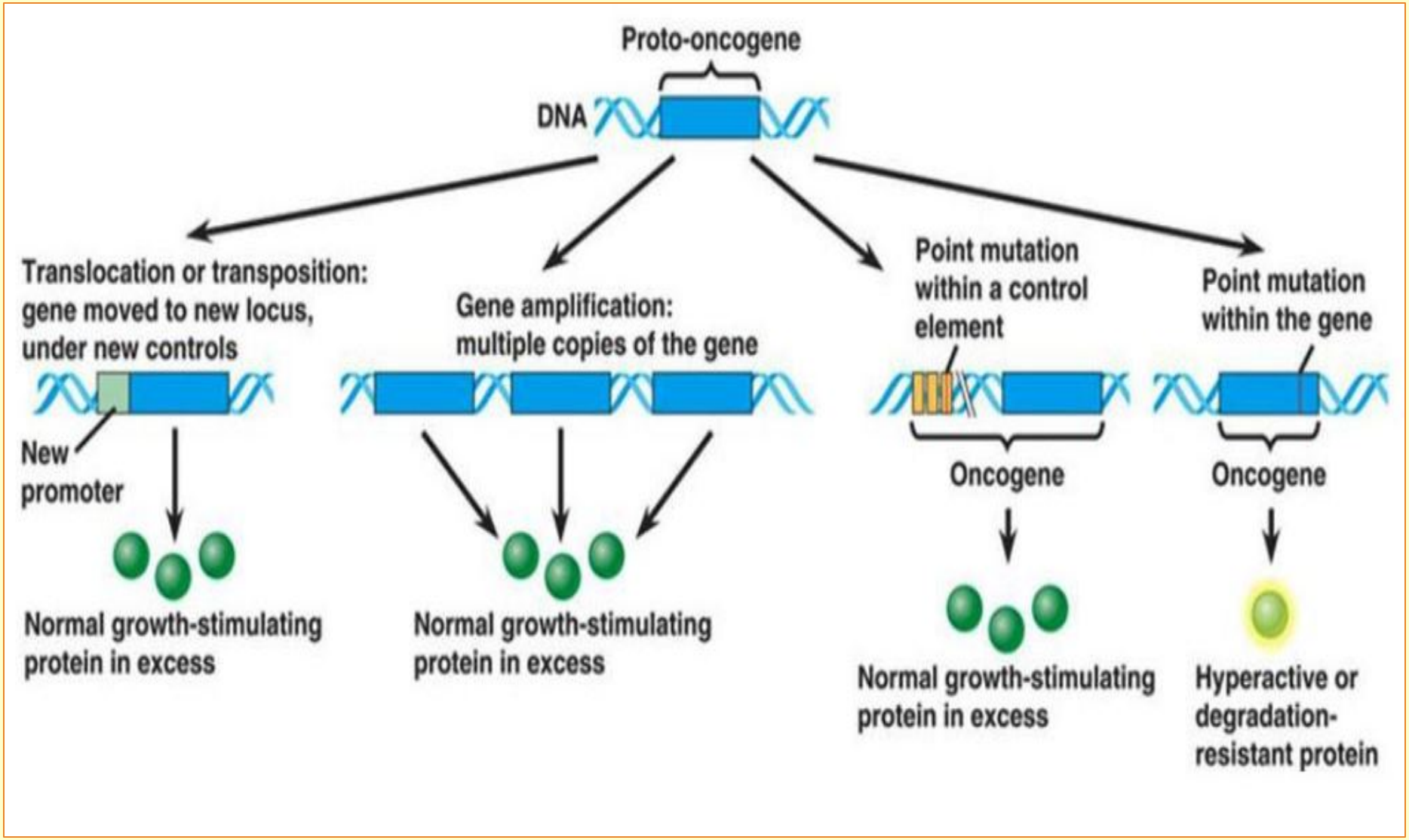
2. Proto-Oncogenes are structural genes as well, because they are responsible for synthesis of proteins and RNAs that perform their vital functions in the cell.

3. Proto-Oncogenes are regulatory genes in view of the essential roles played by their protein/RNAs products in regulating cellular processes programmed and maintained under the supervision of Proto-oncogenes.

Regulatory functions of proto-oncogenes are mediated by their protein/microRNAs products. These products participate in constituting and formation of biochemical networks responsible for performing and controlling these regulatory functions within cells as well as in the extracellular environment.

Mutations of Proto-oncogenes sometimes turn them to Oncogenes. Oncogenes exhibit increased production of these proteins/RNAs, thus leading to increased rate of cell division, decreased differentiation capabilities of cells, inhibition of cell death, and loss of contact inhibition with adjacent cells. Taken together, these phenotypes define the basic and critical aspects of the malignant phenotype which characterizes cancer cells.

Molecular Mechanisms Of Carcinogenesis
Causes & Consequences of Mutations of Proto-oncogenes to Oncogenes



Molecular Mechanisms of Carcinogenesis

1. Point mutations: missense mutations, insertions, deletions, or frame-shifting mutations of the coding regions of proto-oncogenes that lead to synthesis of new proteins with oncogenic activity (onco-proteins).

2. Point mutations, deletions, insertions, or frame-shifting in the promoter region of a proto-oncogene that lead to upregulation, increased transcription, and over production of its protein product(s).

3. Gene duplication/amplification mutational events leading to extra chromosomal copies of a proto-oncogene. Occurrence of these mutations of proto-oncogenes that regulate cell growth and cell division lead to enhanced cell multiplication, hyperplasia, and tumor formation.

4. Chromosomal translocation events that relocate a proto-oncogene to a new chromosomal site. If the new site is downstream of an over-expressive promoter or enhancer site, higher expression of the translocated proto-oncogene and over synthesis of its products can occur.

5. Chromosomal translocations that lead to creation of a new fusion sequence between the translocated proto-oncogene and a second gene. Syntheses of fusion proteins with oncogenic activity might result leading to start of tumor formation and oncogenesis.

Complementary molecular mechanisms involved in tumor development include many mechanisms. Unfortunately, many of them are still obscure. Known complementary mechanisms that participate in carcinogenesis include:

1. Mutation-induced interruption of genome stability. This event might be caused by replicative stress/external mutations leading to double strand breaks (DSB). DSB are major factors in destabilizing the genome with consequent structural/functional disturbances in genome performance. One drastic aspect of these disturbances can be expressed in tumor development and carcinogenesis.

2. Mutations leading to disruption/inactivation/deletion of genes responsible for protection of DNA against structural damage and functional degradation. These genes include DNA repair genes responsible for correction and repair of spontaneous or induced damages and defects in DNA, and Metallothioneins genes which regulate metal homeostasis and play a major role in protecting DNA against heavy metal toxicity and oxidative stress.

3. Mutations leading to disruption/inactivation/deletion of genes that regulate apoptosis. These mutations cause deficiency of apoptosis initiation/completion enzymes and proteins that constitute essential mediators in apoptosis pathways. Pathogenetic arrest of apoptosis results in important quantitative phenotypic features manifested as marked increase in cell numbers and progressive increase in tumor mass.

Arrest of apoptosis or slowing down its predefined rates imparts a selective longer lifespan advantage of cancer cells over normal cells, and positive weight-for-weight balance in favor of cancer cells, availing to them more capabilities for getting nutrients with enhanced survival. Decreased rates of apoptosis is a cardinal feature of the malignant phenotype of most malignant tumors.

4. Mutation-induced over-expression of metastasis genes pave the way for tumors for local spread to neighboring sites and progressive metastasis to distant organs.

Protein products of these genes, e.g. Metalloproteinases genes, have important regulatory functions in maintaining the extracellular environment, inter-cellular contact, and local communication and cooperation pathways between cells and tissues for safeguarding and maintaining the local tissue architecture.

An intact local tissue architecture is a vital and essential anti-metastasis defense mechanism against spread of tumors, and mutation-induced over-expression of genes that keep the integrity of these architectures play a central role in enhancing tumor spread and metastasis

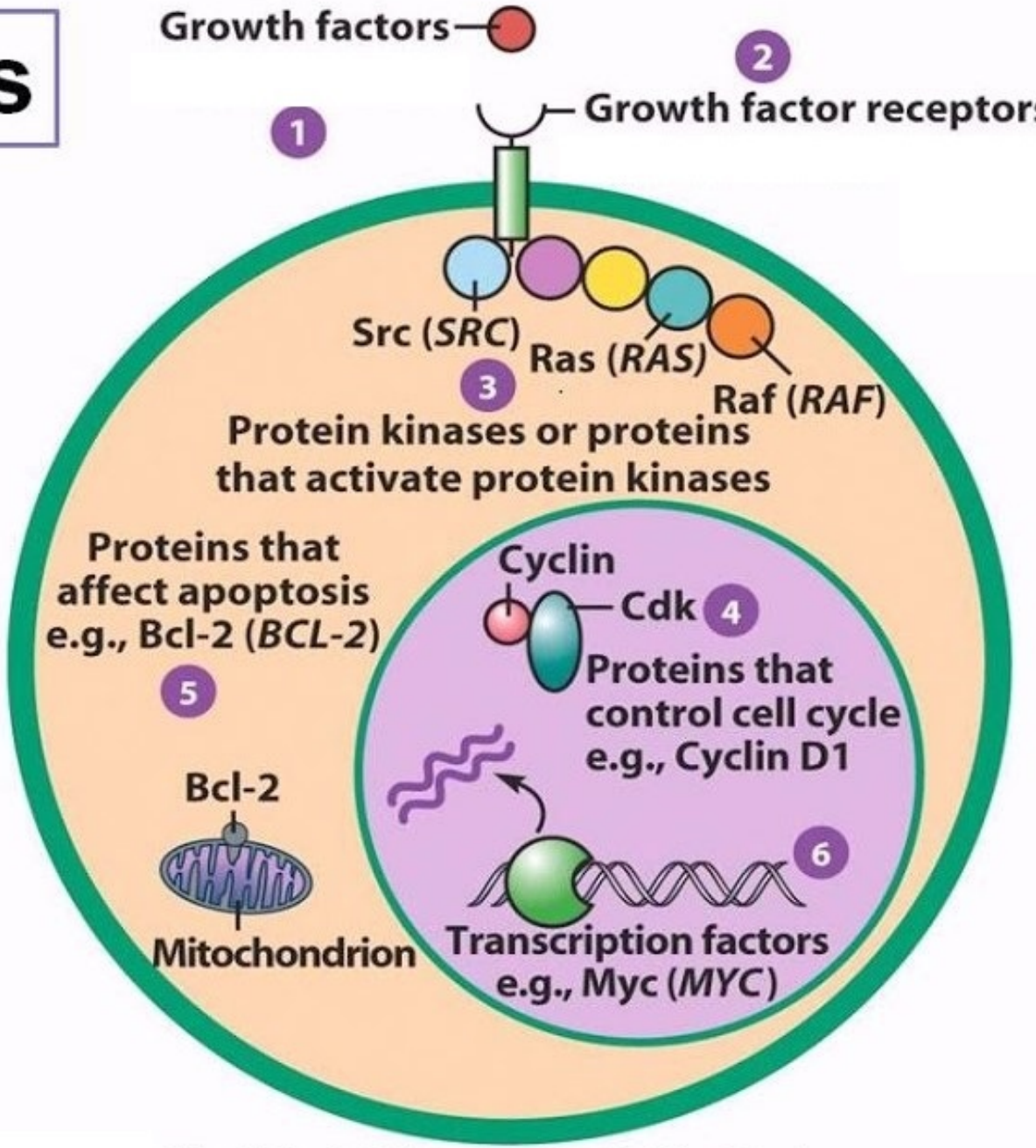
Metastasis is the most drastic consequence and devastating stage of cancer progression. It underlies and dictates the final fate of cancer patients. Without metastasis, cancer would have been a local and localized pathology amenable to total cure by conventional treatment modalities.

Though researches aiming at disclosing the still ambiguous and vague mechanisms that regulate tumor spread and metastasis represent the actual true rational and logical therapeutic approaches for controlling and curing cancer, unfortunately and regrettably they are the least in priority among researches aiming at finding palliative/therapeutic approaches for cancer.

Tumors Initiated by Mutations Inactivating Tumor Suppressor Genes

Gene	Associated Tumor(s)	Gene	Associated Tumor(s)
p53	Brain tumors, Carcinomas of breast, lung, colon, esophagus, liver, colon and rectum. Sarcomas, leukemias and lymphomas.	PTEN	Brain tumors, melanoma, Carcinomas of prostate, endometrium, kidney, and lung.
APC	Carcinomas of Colon and rectum.	NF1	Neurofibrosarcoma
BRCA1	Breast and ovarian carcinomas	NF2	Meningioma
BRCA2	Breast carcinoma	PTC	Basal cell carcinoma
DPC4	Pancreatic carcinoma	WT1	Wilms' tumor
INK4	Melanoma, lung carcinoma, brain tumors, leukemias, and lymphomas	Rb	Retinoblastoma, sarcomas. Carcinomas of bladder, breast, and lung.
MADR2	Colon/rectum carcinoma	VHL	Renal cell carcinoma, Von Hippel-Lindau disease.
PTCH	Medulloblastoma, Basal Cell Carcinoma.	DCC	Carcinoma of stomach and colon.

Oncogenes

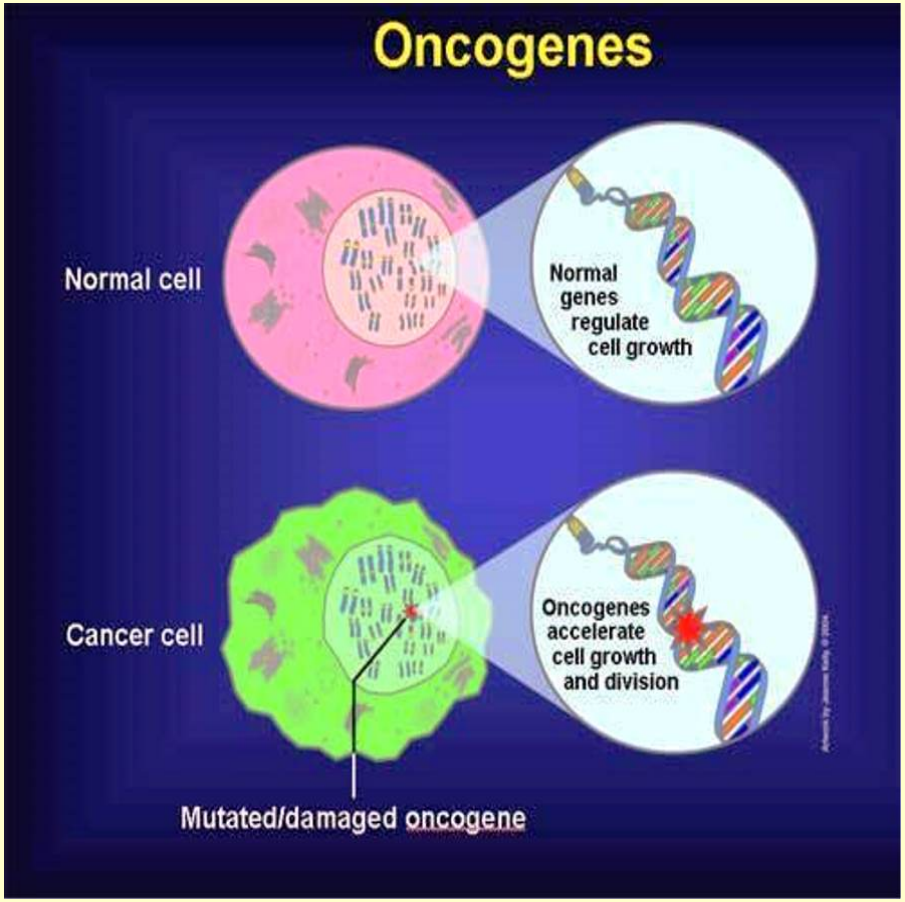


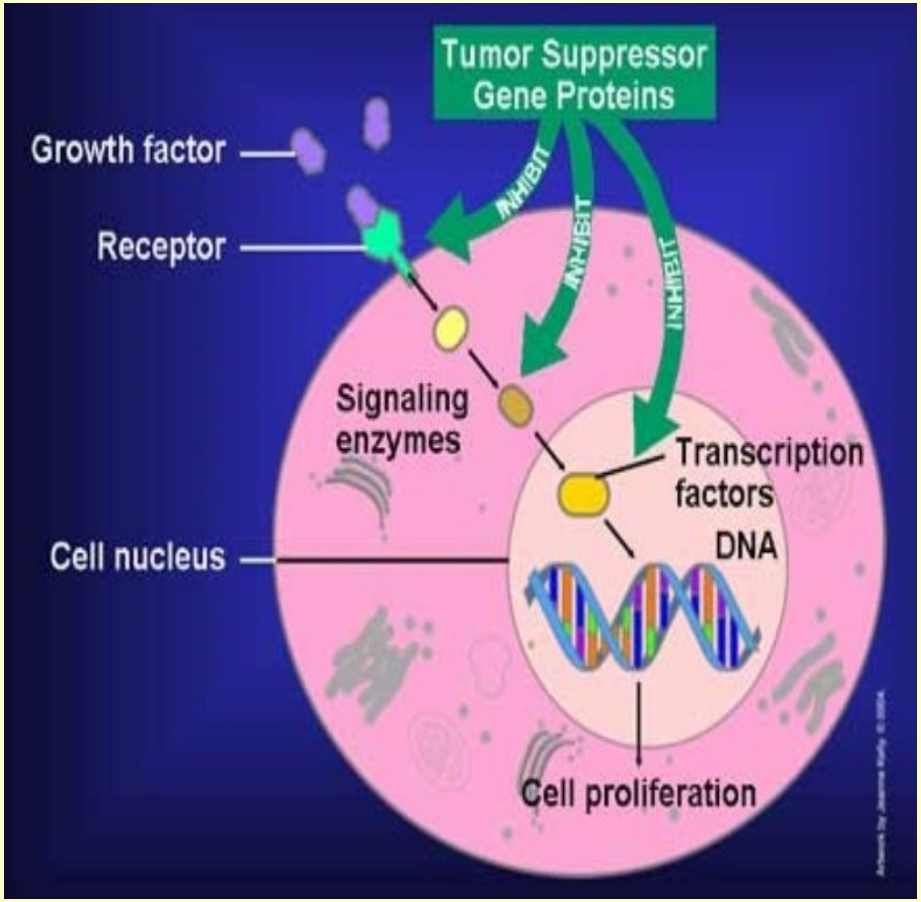
Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

Oncogenes of the human genome			
Category	**Examples**	**Gene function(s)**	**Relevant tumors**
Growth factors, or Mitogens	c-Sis	Induction of cell proliferation.	Glioblastomas, Fibrosarcomas, Osteosarcomas, Breast carcinomas, and Melanomas
Receptor tyrosine kinases	Epidermal growth factor receptor (EGFR), Platelet-derived growth factor receptor (PDGFR), Vascular endothelial growth factor receptor (VEGFR), Human epidermal growth factor receptor 2 (HER2/neu)	Signal transducer for cell growth and differentiation.	Breast cancer, Gastrointestinal stromal tumors, Non-small-cell Lung cancer and Pancreatic cancer.
Cytoplasmic tyrosine kinases	1. Src-family, Syk-ZAP-70 family and BTK family of tyrosine kinases. 2. Abl gene in CML Philadelphia chromosome.	Mediate the responses to, and the activation receptors of cell proliferation, migration, differentiation, and survival	Colorectal and Breast cancers, Melanomas, Ovarian cancers, Gastric cancers, Head and Neck cancers, Pancreatic cancer, Lung cancer, Brain cancers, and Blood cancers.
Cytoplasmic Serine/Threonine kinases and their regulatory subunits	Raf kinase and cyclin-dependent kinases (through overexpression).	Involved in organism development, cell cycle regulation, cell proliferation, differentiation, cells survival, and apoptosis	Malignant melanoma, Papillary thyroid cancer, Colorectal cancer, and Ovarian cancer
Regulatory GTPases	Ras protein	involved in signalling a major pathway leading to cell proliferation	Adenocarcinomas of the pancreas and Colon, Thyroid tumors, and Myeloid leukemia.
Transcription factors	myc gene	Transcription Regulator of genes that induce cell proliferation.	Malignant T-cell lymphomas and Acute myeloid leukemias, Breast cancer, Pancreatic cancer, Retinoblastoma, and Small cell lung cancer.

Mechanisms Of Action Of Oncogenes

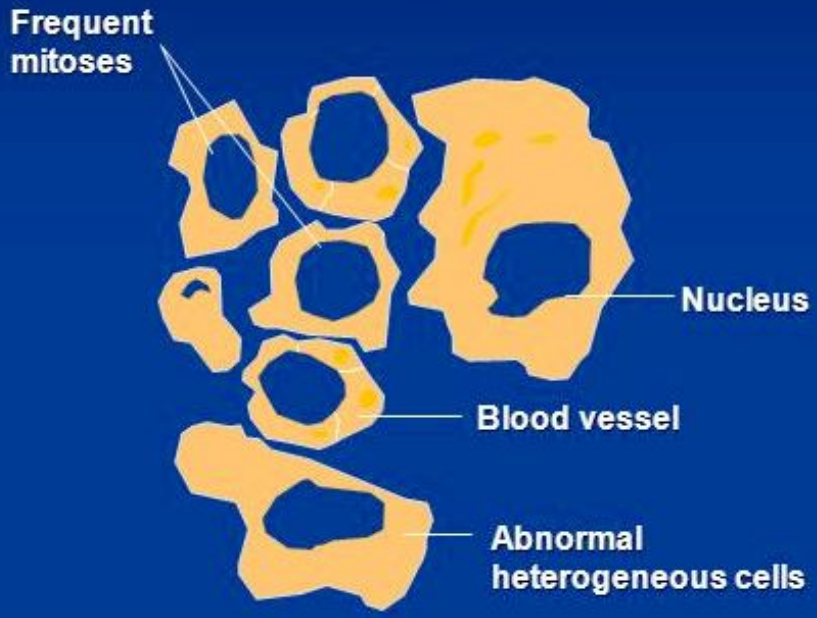
Mechanisms Of Action Of Tumor Suppressor Genes





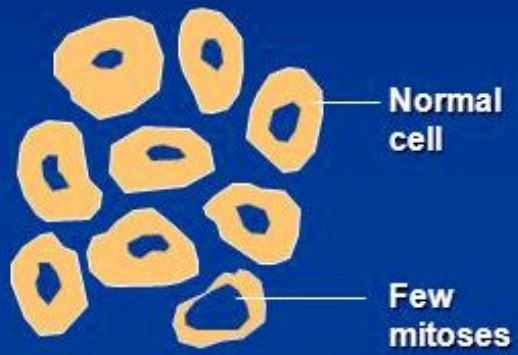
Functional Aspects Of Carcinogenesis

CANCER CELLS



- Loss of contact inhibition
- Increase in growth factor secretion
- Increase in oncogene expression
- Loss of tumor suppressor genes

NORMAL CELLS



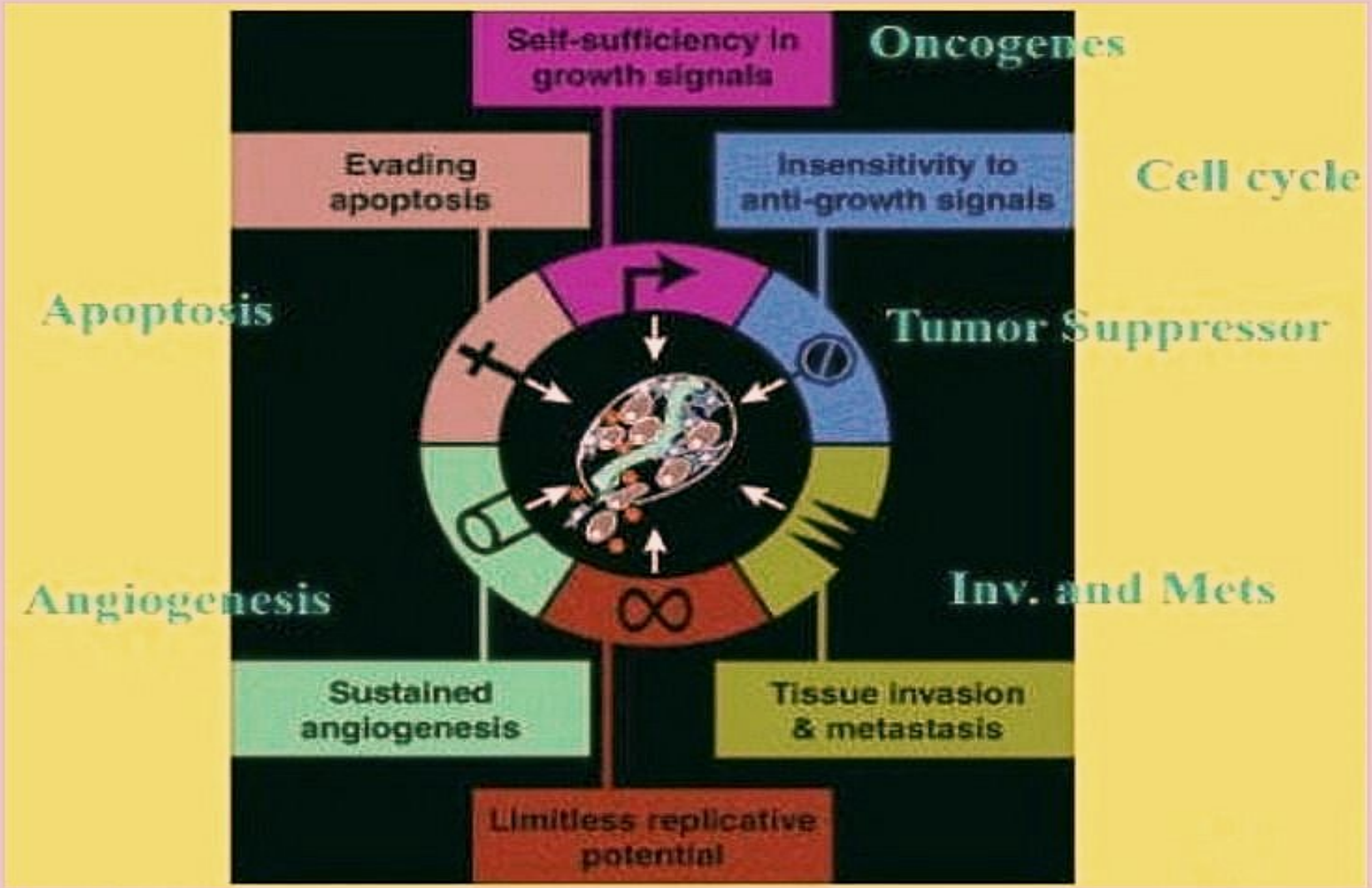
- Oncogene expression is rare
- Intermittent or co-ordinated growth factor secretion
- Presence of tumor suppressor genes

The malignant phenotype

Structural features and functional properties that constitute the malignant phenotype include:

1. **Induced or spontaneous mutations of specific oncogenes and/or tumor suppressor genes.**
2. **Defective repair mechanisms of mutated genes.**
3. **Loss of control of cell cycle leading to unrestrained cell division and hyperplasia.**
4. **Altered pathways of apoptosis resulting in immortality of malignant cells.**
5. **Modification of inter-cellular connections and adhesion molecules leading to loss of contact inhibition mechanisms.**
6. **Induction of angiogenesis.**
7. **Increased dependence on Glycolysis.**
8. **Epithelial-mesenchymal transition of cancer cells.**
9. **Invasion of surrounding tissues and metastasis to distant sites.**

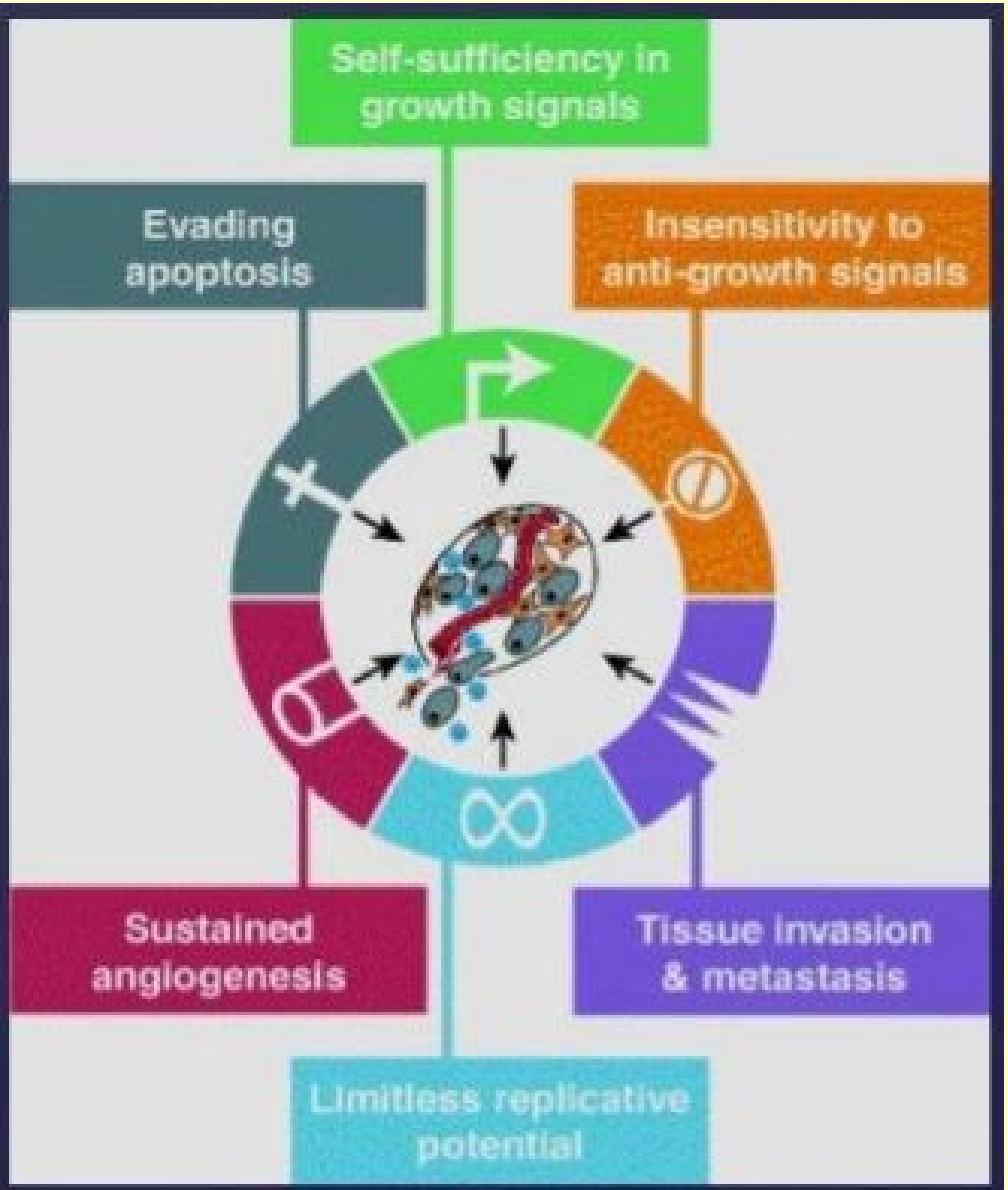
Functional Aspects Of Malignant Transformation



The Malignant Phenotype

1. Self sufficiency
2. Insensitivity to growth inhibitory signals
3. Evasion of apoptosis.
4. Limitless replicative potential.
5. Angiogenesis
6. Invasion & Metastasis

7. Defect in DNA repair.



Critical aspects of the malignant phenotype

The marked similarity of the phenotype of malignant cells to that of early embryonic and fetal cells represents an essential clue to understand and interpret the nature of the genetic alterations involved in the process of malignant transformation. This similarity comprises the general cardinal properties of tumor cells including enhanced rate of cell division, mass expression/suppression of large number of genes, resilience and plasticity of the cytoskeleton allowing cell dissemination/migration and metastasis, augmented potential of differentiation/specialization/growth and, most importantly, altered pathways of apoptosis which allow for longer survival of cancer cells with consequent potentiation of the functional profile of the malignant phenotype. This hazardous result of halted or reduced apoptosis in malignant cells plays a critical role in conferring the aggressive behavior upon the cells and in maintaining tumor growth/progression and metastasis, which is the main culprit responsible for the dreadful end of cancer patients.

Imprinting Defects In Carcinogenesis

Widespread selective temporal imprinting of genes after mediation and completion of specific developmental processes occurs normally and is maintained in post-natal life as long as no need for the synthetic and/or the regulatory roles of imprinted genes arises.

Each tissue, and cell type, has its selective temporal imprinting pattern according to their roles in normal physiological processes. For instance, all genes of hepatocytes except those needed for liver cell functions are imprinted after differentiation of liver cells.

Loss of temporal imprinting of genes is a major feature of malignant transformation. It allows reactivation of large numbers of imprinted genes in transformed cancer cells

and synthesis of large numbers of proteins not normally produced by the differentiated cells. This feature allows cancer cells of specific organ to express functions of other organs, e.g., synthesis of blood cells by lung cancer cells. It also allows for the acquisition by the malignant cells of greater advantageous potentials compared to normal cells. This feature underlies the development of the wide-spectrum of the morphological and functional aspects of the malignant phenotype that characterizes cancer cells.

Molecular mechanisms of tumor metastasis

Although the enigmatic phenomenon of tumor metastasis is responsible for the lethality of the vast majority of tumors, the nature of the pathogenetic mechanisms underlying and mediating metastasis of malignant cells are, still, poorly understood.

Selective genomic reactivation and/or suppression of genes responsible for regulating cell movement, cytoskeleton modifications and intercellular adhesions resulting in reversion to the early embryonic/fetal stage where cell migration to, and localization in, distant organs plays a crucial role in organogenesis, undoubtedly, has a central regulatory role in tumor metastasis.

Functional Aspects of Matrix Metalloproteinases

- MMPs → Collagenases
  Gelatinases
  Stromelysins and
  Membrane-type metalloproteinases.

- Physiological roles

Apoptosis
Ovulation
Inflammation
Angiogenesis
Bone remodeling
Mammary gland development
Embryogenic remodeling
Organ morphogenesis

Pathological roles

Diseases of CNS
Cardiovascular diseases
Lung fibroblastic disease
Liver fibrosis
Diseases of bone
Tumor development and metastasis

Roles of Matrix Metalloproteinases (MMPs) in Tumor Spread, Invasion and Metastasis

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endoproteinases whose enzymatic activity is directed against components of the extracellular matrix (ECM). In addition to their many important physiological functions, MMPs induce and facilitate tumor cell invasion and metastasis by at least three distinct mechanisms:

First: the proteolytic action of these proteinases, oftenly found at the invasive front of the tumor, removes the physical barriers to invasion through degradation of ECM macromolecules, e.g., proteoglycans, collagens, laminins.

Second: MMPs modulate the adhesion properties of malignant cells, allowing them to move through the ECM.

They help cancer cells to form new cell-matrix and cell-cell attachments and to break existing ones. The actions of MMPs induces significant variations in the adhesive phenotype of tumor cells, which is a preliminary step for invasion, progression and metastasis.

Third: MMPs may act on ECM components or other proteins to uncover hidden physiological activities. For example, the angiogenesis inhibitor angiostatin may be produced from plasminogen by MMP action, and laminin-5 is specifically degraded by MMP-2 to produce a soluble chemotactic fragment. Thus MMPs play multiple key roles in facilitating the metastasis of tumor cells via many mechanisms including tumor-induced angiogenesis, tumor invasion, and establishment of metastatic foci at the secondary site.

In view of these critical roles in cancer, therapies designed to interfere with specific MMP actions may be useful in the control of metastatic disease.

Anti-Metastasis Mechanisms

In opposition to factors that facilitate spread, invasion, and metastasis of tumor cells, there are a lot of other defense mechanisms that act to hinder and suppress tumor spread. These mechanisms include:

1. Metastasis suppressor genes

These genes produce specific proteins that act in a variety of ways to suppress and arrest metastasis. Examples include genes that induce synthesis of TIMP or tissue inhibitors of metalloproteinases, e.g., CAD1 gene.

2. Host immune responses

These arise in response to proteins synthesized by cancer cells and involve activated macrophages, cytotoxic lymphocytes and natural killer cells.

3. Oncostatic and anti-metastasis roles of Melatonin

Melatonin is a hormone secreted by the pineal gland and is the main regulator of the circadian rhythm, or the biological clock, that coordinates the physiological and psychological processes with daytime changes. Melatonin has vital diverse functions including effective protection of cells against radiation-induced chromosome breakage, and inhibition of tumor development induced by chemical carcinogens in animals. Melatonin exhibits a variety of oncostatic properties and metastasis suppressing and arresting effects in many types of tumors during different stages of their progression. The anti-mutagenic and anti-clastogenic functions of Melatonin may play a role in suppressing early stages of carcinogenesis triggered by mutations-induced genomic damage.

Clonal origin of tumors

There are two main concepts regarding the cellular origin of cancer. The hypothesis of the monoclonal origin of tumors proposes that most neoplasms arise from a single cell of origin, and tumor progression results from acquired genetic variability within the original clone allowing sequential selection of more aggressive sublines of the mother cell. Within the context of this hypothesis, carcinogenesis is considered as a progressive multistage pathophysiological process induced by pathogenetic mechanisms leading to malignant transformation of one single cell turning it into cancer cell and spreading to its daughter progeny resulting in formation of a tumor.

The opposing hypothesis, the polyclonal origin of tumors, attributes tumor development to a situation where two or more cells or clones of cells interact and cooperate to initiate radical genomic alterations leading to consequent proteomic changes with gradual progressive acquisition and expression of the malignant phenotype and formation of a tumor.

This postulation rests on a number of findings most relevant of which is the observation that while tumors have higher levels of mutation than normal tissues, cells with oncogenic mutations frequently are present as subpopulations within tumors, rather than as the pure mutant populations expected to develop from a single initiated cell.

It is hard to accept the postulation of tumor development from a single normal cell that gets transformed into a malignant cell by one or few mutations affecting one or more cancer-related genes of the genome. The malignant phenotype is not a result of just few mutations, rather it reflects a radical widespread structural and functional change and reprogramming of the genome.

There are too many reasons for this conclusion:

First, whereas most mutations result in deleterious functional consequences of affected cells including loss of cellular functions, induction of apoptosis and accelerated degeneration and cell death, none of these detrimental effects are observed in cells undergoing malignant transformation.

Instead, malignant transformation of normal cells to cancer cells results in acquisition by cancer cells of new functional and morphological phenotypes encompassing numerous selective advantages over normal cells.

Second, the large scale extensive structural/functional genomic alterations of the magnitude seen in normal cells undergoing malignant transformation can not be caused by, or solely attributed to, one or few mutations.

Third, the obvious purposeful nature of malignant transformation of normal cells to cancer cells coincides with the conventional rules of biological evolution, taking into consideration the numerous selective advantages conferred upon malignant cells as regards metabolic competence, higher proliferative potential, enhanced regenerative abilities, survival span and many others.

Although a paradoxical fate of cancer cells finally ensues leading to extinction rather than preservation, expansion, or evolution of the genome, this happens because of devastating complications related to the whole organism, e.g., under nutrition, immunodeficiency and organ failure, and does not change the biological observations revealing that cancer or malignant transformation represents a positive selective advantageous evolutionary stage of biological life of normal cells undergoing evolutionary transitions to cancer cells.

The evolutionary paradox of cancer

A strictly defined framework regulate the three main life-sustaining constituents of the cell, viz. the genome, the transcriptome and the proteome. This regulation aims at preservation of the three main features of biological life, viz. genetic integrity, genetic stability and genetic identity. The behavior of malignant tumors is conceivable and clearly interpretable within the context of biological evolution as acquisition of new phenotypes with selective advantages over current phenotype, proliferation, spread, suppression of apoptosis, metastasis and formation of new tumors at multiple sites can be looked at as persistent trials to expand the size of the genome and to improve its survival potential, compared to mother cells.

Paradoxically, in contrast to expected evolutionary improvements, the behavior of malignant cells results in deleterious effects on the organism leading to loss of integrity of the genome as observed in occurrence of marked hypodiploidy/hyperdiploidy of tumor cells, loss of genomic stability caused by, and observed as, small and large deletions/enhanced rates of chromosomal rearrangements/breaks and structural aberrations detected in most cancer cells during most of their life spans, as well as loss of genomic identity due to acquisition of new different distinctive phenotypes that bear little resemblance to those of the parent phenotypes and that get more divergent along their progressive course of spread and survival.

There is no satisfactory explanation of this evolutionary paradoxical fate of malignant cells characterized by final extinction in spite of the marked selective advantages they have over normal cells. Also, there is no indication of possible formulation of such an interpretation in the near, or even in the far, future. Compared to apoptosis, which represents molecular biological mechanisms responsible for terminating life at the cellular level, cancer may be looked at as the biological mechanism responsible for terminating life of the whole organism.

www.archive.org/details/MedicalGenetics